Fortnightly Review

Drug treatment of Parkinson's disease

Niall Quinn

The management of a chronic, progressive neurological disorder such as Parkinson's disease requires much more than drugs. Equally important are education and support of patients (in conjunction with the Parkinson's Disease Society); the timely provision of occupational and speech therapy and physiotherapy; and dietetic and social work input.[1] Ideally management should be by a multidisciplinary team linking specialist Parkinson's disease clinics to health centres, and increasingly incorporating the services of specialist nurse-practitioners. In addition, surgical approaches to treatment are enjoying a renaissance.[2] Nevertheless, a wide range of effective drugs are available for treating Parkinson's disease. Optimum treatment demands familiarity with the available drugs and how best to use them.

Summary points

- A wide variety of drugs is available for treating Parkinson's disease, including anticholinergics, amantadine levodopa, dopamine agonists, and selegeline
- In younger patients (<50) levodopa is usually delayed provided that adequate relief of symptoms can be achieved with other drugs. In older patients (>70) levodopa should be started as soon as symptom relief is required. Between these ages there is no consensus, but at present most such patients should probably be given controlled release levodopa before a dopamine agonist is added
- Fluctuations can often be alleviated by giving controlled release preparations of levodopa, by giving small doses at frequent intervals, by adding selegiline or a long acting oral agonist, or by subcutaneous apomorphine
- Dyskinesia can be peak dose, diphasic, or "off period." The diphasic form is hardest to alleviate
- Psychiatric side effects should initially be managed by changing the antiparkinsonian treatment before resorting to antipsychotic drugs

Available drugs

ANTICHOLINERGICS

The anticholinergic drugs most commonly used to treat Parkinson's disease in the United Kingdom are benzhexol (usual dose about 2 mg three times a day) and orphenadrine (50-100 mg three times a day). These drugs have a mild antiparkinsonian effect, and are said to be more effective for tremor than for the other features of parkinsonism. Nevertheless, patients can worsen considerably if long term anticholinergic treatment is rapidly withdrawn so, except in emergencies, these drugs should always be stopped gradually.

Anticholinergics can cause blurred near vision due to mydriasis (so they are contraindicated in narrow angle glaucoma), give a dry mouth (sometimes desirable if sialorrhoea is a problem), precipitate acute retention of urine in men with prostatic enlargement (but also help frequency and urgency due to the detrusor hyperreflexia that is common in Parkinson's disease), and can cause or worsen constipation. They may worsen choreiform dyskinesia and lessen some dystonic side effects of levodopa. The most serious side effects, however, are neuropsychiatric. The drugs can worsen frontal symptoms, affect memory and concentration,[3] and precipitate an organic confusional state with visual hallucinations. Patients with cognitive impairment and those taking several drugs are particularly vulnerable to these problems, so anticholinergics should be avoided in elderly or dementing patients.[4]

AMANTADINE

Amantadine is another mild antiparkinsonian drug. The usual dose is 100 mg twice daily but this must be reduced if renal impairment is present. Side effects can include livedo reticularis, ankle oedema, and, rarely, confusion.

LEVODOPA

Since dopamine does not cross the blood-brain barrier, it is replaced by giving its precursor levodopa, which does. To prevent the metabolism of levodopa to dopamine outside the brain, which wastes much of the ingested dose and often causes nausea and vomiting, levodopa is combined with a peripheral decarboxylase inhibitor that does not cross the blood-brain barrier. Several dose sizes and formulations are available (table I). Levodopa is absorbed from gut to plasma (mainly in the proximal small bowel) and transferred from plasma to brain, by the active transport mechanism for large neutral amino acids.

As well as occasional early nausea or vomiting, to which tolerance usually develops rapidly, the side effects of levodopa can include postural hypotension, aggravation of peptic ulcers, sweating attacks, and dark discoloration of urine and sweat. The most problematic adverse effects are the motor fluctuations and dyskinesia that constitute the long term levodopa syndrome (see later) and neuropsychiatric symptoms. Finally, although concerns have been voiced about the theoretical possibility that levodopa could accelerate

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BMJ 1995;310:575-9

TABLE I—*Available preparations of co-careldopa and co-beneldopa*

Drug	Carbidopa (mg)	Levodopa (mg)	Benserazide (mg)
Co-careldopa*:			
Sinemet 275	25	250	
Sinemet CR 250†	50	200 (140)	
Sinemet plus 125	25	100	
Sinemet 110	10	100	
Half sinemet CR†	25	100 (70)	
Sinemet LS	12·5	50	
Co-beneldopa‡			
Madopar 250		200	50
Madopar 125		100	25
Madopar CR†		100 (70)	25
Madopar 62·5		50	12·5

*All Sinemet preparations are tablets, and all but "half Sinemet CR" are scored. Breaking a CR250 in half alters its release characteristics towards the standard preparation.

†The relative bioavailability of levodopa in controlled release preparations (in brackets) is about 70%.

‡All Madopar strengths are in capsule form, but the 125 and 62·5 strengths are also available as scored tablets of a dispersible preparation that is absorbed, and hence works, faster than a standard preparation.

the disease process, there is no conclusive evidence to support this view.

DOPAMINE AGONISTS

These drugs act directly on dopamine receptors. Since they act in the periphery as well as centrally, they often cause initial sickness by stimulating dopamine receptors in the vomiting centre in the medulla, which is functionally outside the blood-brain barrier. Unlike other anti-emetics, which all worsen parkinsonism, the peripherally acting dopamine receptor blocker domperidone (usual dose 20 mg three times a day) can prevent, reduce, or abolish sickness without blocking striatal receptors. All agonists can cause postural hypotension, and all cause psychiatric side effects more commonly than levodopa. Unlike levodopa, dopamine agonists sometimes cause vasospasm, erythromelalgia, ankle swelling, and (rarely) pleuropulmonary or retroperitoneal fibrosis.

Three oral dopamine agonists are available. Pergolide has the longest motor benefit (four to six hours) and stimulates D_1 and D_2 dopamine receptors. Bromocriptine acts for about three to five hours, and is a D_2 receptor agonist with weak D_1 antagonist effects. Lisuride has the shortest duration of action (two to four hours) and is mainly a D_2 agonist. The absolute potency of these drugs is less than that of levodopa: 1 mg of lisuride or pergolide is roughly equivalent to 10 mg of bromocriptine or 100 mg of levodopa plus peripheral decarboxylase inhibitor.

Apomorphine is also a D_1 and D_2 receptor agonist but is given parenterally. It has an equivalent potency to levodopa. Possible side effects are as for levodopa, with the addition of yawning, drowsiness, and local skin reactions or abscesses at injection sites.

SELEGILINE

Selegiline is a selective inhibitor of monoamine oxidase type B, which is one of the enzymes that catabolise dopamine in the brain. Given alone, it has almost no adverse effects, although metabolism to methamphetamine sometimes causes insomnia. When given together with levodopa it can smooth out early wearing off, but it can also provoke or worsen dyskinesias or psychiatric side effects.

CATECHOL *O*-METHYL TRANSFERASE INHIBITORS

Another enzyme that metabolises levodopa and dopamine is catechol *O*-methyl transferase. Two inhibitors of this enzyme are currently under clinical trial: entacapone, which acts peripherally,[5] and tolcapone, which also acts centrally.[6] Both have an (apparent) dose sparing effect, and prolong the plasma half life of levodopa and thus its clinical effects.[5,6]

How to use the drugs

Many aspects of the drug treatment of Parkinson's disease are still controversial and based on empirical experience, since there have not been enough properly designed clinical trials. What follows is my own current approach, not all elements of which necessarily meet with universal agreement.[7]

Early treatment

The first decision is whether to treat the symptoms of a patient with early, relatively mild disease. The decision is taken jointly by the patient and the doctor, whose role is to explain the available options and their advantages and drawbacks. It requires consideration of the patient's personal situation (for example, is employment threatened?) and expectations. The doctor should explain at the outset that, although a range of effective symptomatic treatments exists, none is perfect and that the condition will probably become more difficult to manage the longer the patient has had the disease and has been taking drugs (these two factors being inextricably linked).

If symptomatic treatment is not yet needed or wanted neuroprotection should be considered. At present no drug has a proved neuroprotective effect in Parkinson's disease. Selegiline, which blocks the conversion of the protoxin 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) to the nigral toxin 1-methyl-4-phenylpyridinium species (MPP+), prevents MPTP-induced parkinsonism in animals. A large double blind placebo controlled trial in North America in 800 patients with early, untreated Parkinson's disease showed that selegiline does delay the need for levodopa therapy, by about nine months on average, and that vitamin E 2000 IU/day has no effect.[8] However, we now know that selegiline gives mild symptomatic benefit in most patients,[9] so it is not clear whether its effect in the trial was partly neuroprotective and partly symptomatic or wholly symptomatic. Nevertheless, in younger subjects I give the patient and the drug the benefit of the doubt because, even if the mechanism turns out not to be neuroprotective, selegiline still delays the need for levodopa, which may be desirable.

If treatment of symptoms is required the age and cognition of the patient will influence the choice of drugs (table II). Younger patients develop fluctuations and dyskinesia to a more severe degree, and sooner, after starting levodopa treatment[10,11]; they may require drug treatment for decades; they can better tolerate multiple drugs; and dementia is uncommon.[10] In contrast, older patients develop motor complications to a milder degree and later after starting levodopa[11]; they may succumb to other diseases or to old age before developing them; they are less tolerant of multiple drugs; and many have cognitive impairment and are therefore particularly liable to develop cognitive or neuropsychiatric complications of treatment, especially with anticholinergic drugs.

Although these observations are all generally

TABLE II—*Differences between young and old patients with Parkinson's disease*

	Young (<50 years)	Old (>70 years)
Fluctuations	Early, severe	Late, mild
Dyskinesia	Early, severe	Late, mild
Life expectancy	Decades	Years
Cognitive impairment	Rare	Common
Anticholinergics	Well tolerated	Poorly tolerated
Multiple drugs	Well tolerated	Poorly tolerated

accepted, age and cognitive decline are continua. Arguments for or against delaying levodopa might seem clear when comparing a 40 year old and 80 year old patient, or even patients under 50 and over 70. However, for those aged 50-70 (the mean age of onset of Parkinson's disease is about 60), the issue becomes much less clear. I will therefore state a general position on "young" versus "old" patients (fig 1) and encourage more flexibility in patients aged 50-70.

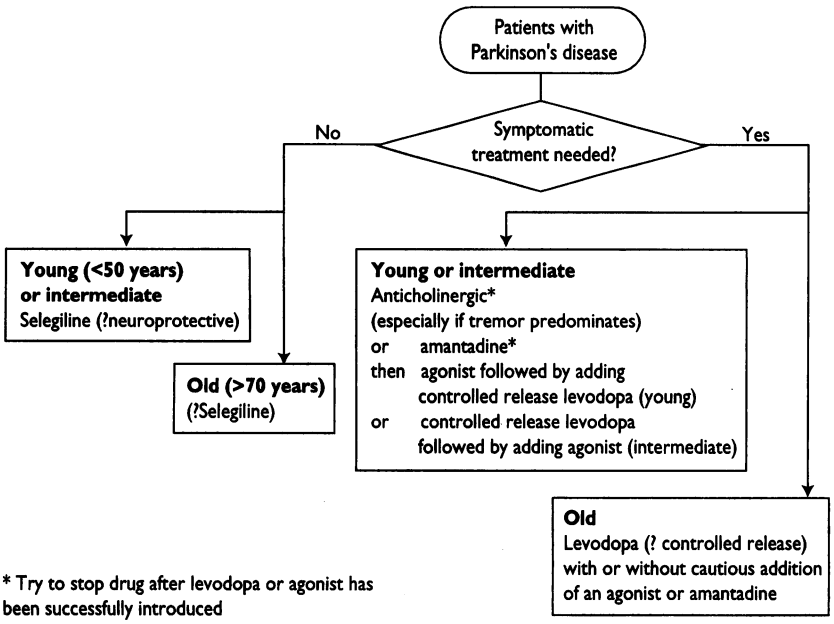
YOUNG PATIENTS (AGE <50 YEARS)

I try to delay levodopa in patients under 50 if possible so I generally give selegiline first. If the disease is mild, amantadine or an anticholinergic can give modest benefit. Alternatively, or when the above drugs are not helping enough, I prescribe a dopamine agonist, initially with domperidone cover. The agonist dose should be gradually increased up to 1 mg three times a day (pergolide or lisuride) or 10 mg three times a day (bromocriptine), or higher if the patient can tolerate it. After some months or a year or two a levodopa preparation will usually need to be added because the agonist does not sufficiently control symptoms. However, among the 5-10% of patients (more if higher doses are reached) who can be maintained on agonist monotherapy for up to five years dyskinesia is exceptionally rare, fluctuations are uncommon, and levodopa can be delayed.[12-15] Even after the delayed addition of levodopa dyskinesia is still less common than if levodopa had been started earlier, and fluctuations are delayed.[16] Similar advantages have also been claimed for early combination therapy,[15 17] that is, either starting both drugs together or starting levodopa first but adding an agonist when the dose reaches about 400 to 600 mg daily, as part of a levodopa sparing policy. However, this approach remains controversial.[18]

An important proviso exists to this approach of gradually working through and slowly titrating the doses of non-levodopa drugs. Patients who might respond to levodopa may not respond at all, or inadequately, to agonists, or it may take months to obtain adequate benefit. If rapid response is essential—for example, because the patient's job is threatened—younger patients may opt for early levodopa treatment. Levodopa can also be prescribed as a diagnostic aid if non-idiopathic disease is suspected.

OLD PATIENTS (AGE >70 YEARS)

In patients over 70 I start levodopa as soon as treatment of symptoms is needed. Unless the patient holds strong views, I do not usually prescribe selegiline. I avoid anticholinergics, and I use amantadine and dopamine agonists with caution. Patients with dementia who need antiparkinsonian treatment should have only levodopa. The dose should be set at the lowest that gives a compromise between immobility and confusion or hallucinations.



* Try to stop drug after levodopa or agonist has been successfully introduced

FIG 1—*Early treatment of Parkinson's disease*

INTRODUCING LEVODOPA

Standard formulations of levodopa (usually started thrice daily) produce rapid, excessive plasma peaks, followed by troughs, of levodopa concentration. This results in the brain being alternately flooded and starved of dopamine throughout the day. Sooner or later (principally because of central pharmacodynamic changes) the patient's motor state also fluctuates thrice daily. Continuous, rather than intermittent, dopamine receptor stimulation might be more physiological,[19] and trials of controlled release formulations to see whether they delay or reduce dyskinesia and fluctuations are in progress. I usually introduce levodopa as a controlled release preparation[20 21] in younger patients and use the lowest dose of levodopa that will give acceptable benefit.

The management of treatment related complications

After an initial "levodopa honeymoon," when symptoms are smoothly controlled throughout the day, at least half of patients with Parkinson's disease develop motor fluctuations or dyskinesia (unwanted drug induced involuntary movements) within the first five years of treatment.[22 23]

FLUCTUATIONS

The first sign of fluctuation may be early morning akinesia, when the effect of the previous tea time dose has worn off by the next morning. The patient next notices a gradual, undulating pattern of wearing off, or end of dose deterioration, with slowness or tremor returning when the next dose of levodopa is due. This is commonly managed by giving levodopa more frequently, simultaneously reducing the size of the doses to avoid overdosage, which may provoke or worsen dyskinesia.

Partially substituting standard levodopa by controlled release formulations may be an alternative to dose fractionation, particularly in patients with early fluctuations.[20 21] Controlled release preparations are more difficult to use, so careful planning and perseverance are necessary to obtain optimal results. Their bioavailability (total amount of drug absorbed from an ingested dose) is variable, but averages about 70% of that of standard preparations. Although the higher, longer "tail" with controlled release preparations is desirable (but can lead to problems of levodopa accumulation), the initial absorption is much slower (leading to delayed action) and the peak concentration is lower (increasing the chances of dose failure (fig 2)). Patients with fluctuations may therefore need small additional kick start doses of standard levodopa, especially with the first controlled release dose of the day. Although fluctuation can be controlled in some patients with five or even six hourly doses of controlled release levodopa, most seem to need four hourly, to even three hourly, doses. Other treatment approaches are to add selegiline or to add, or partially substitute for levodopa, an agonist drug with a more prolonged action. A dose of controlled release levodopa or an agonist on retiring to bed can improve night time mobility and hence sleep.

With time the fluctuations may become more abrupt and of greater amplitude, so that some patients are precipitated within minutes, or even seconds, from a

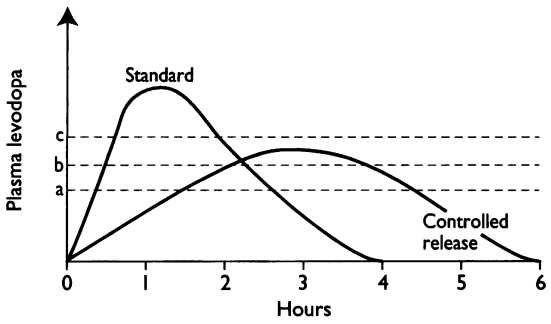


FIG 2—*Stylised representation of potential problems using controlled release levodopa alone compared with standard preparations for different thresholds of levodopa required to turn on*

Threshold a: Patient turns on later after controlled release but on duration is longer than with standard treatment

Threshold b: Patient turns on even later after controlled release and sometimes not at all, with on duration similar to that after standard preparation

Threshold c: Patient turns on only after standard preparation

state of dyskinetic mobility (on) to one of profound rebound parkinsonism (off). A threshold effect often emerges simultaneously, whereby a dose of levodopa is either sufficient to relieve symptoms or completely fails to work (fig 2). Clearly the smaller the individual dose, the greater the probability that the concentration of dopamine in the brain will hover about a critical level. Thus, small changes in levodopa concentration due to variations in gastrointestinal motility or to competing amino acids from protein in the diet,[24 25] may have consequences out of proportion to their magnitude, increasing the chances and unpredictability of dose failure or latency. Confining protein intake to the evening meal may help in some patients.[25] If off periods predominantly occur at certain times, try increasing the preceding dose of levodopa or adding an oral agonist at that time.

If fluctuations remain problematic subcutaneous administration of apomorphine may reduce the number of hours spent off in selected patients.[26] Most patients inject single doses when turning off or when off, although when off they may be so immobile that a carer has to inject them. The big advantage of apomorphine is its reliability: patients almost always get relief within 15 minutes, often sooner, making it invaluable as a rescue device. Unfortunately, the on period usually last only 40 to 70 minutes. This short half life can be overcome by continuous daytime administration of apomorphine through a portable pump. In some, but not all, patients the use of apomorphine may make it possible to reduce the daily dose of levodopa.

Reliable patient feedback is essential for making rational treatment decisions. When patients are reviewed in clinic they should be talked through an average day (fig 3). Some patients are also able to keep accurate "on-off" diaries over a few weeks.

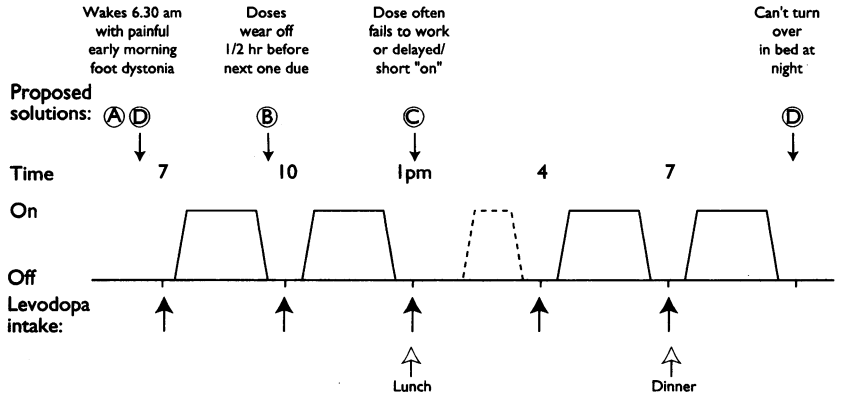


FIG 3—*Average day of patient with Parkinson's disease experiencing fluctuations. Alterations to treatment might include taking first levodopa dose as dispersible preparation at 6 30 am: (A) and staying in bed until it works or starting the day with an apomorphine injection. (B) try 2½ hourly dosing, introducing controlled release levodopa, or adding oral agonist or injected apomorphine. (C) Improve afternoon by delaying protein intake until evening or increasing lunchtime levodopa dose. (D) Take controlled release preparation or agonist on retiring to bed.*

DYSKINESIAS

Levodopa induces three main types of dyskinesia:

Peak dose dyskinesia can simplistically be viewed as an overshoot phenomenon, the replacement of akinesia (too little movement) by dyskinesia (too much) at times when the dose is working well. The dyskinesia is usually painless and comprises choreic or mobile dystonic movements, or both, mainly affecting the limbs. Initially it may occur only at the peak of effect and lessen on reducing the dose. However, later the dyskinesia may become indistinguishable from benefit (square wave dyskinesia), so that the patient is either on and dyskinetic or off and immobile. Peak dose dyskinesia is not seen with de novo agonist monotherapy, and when it occurs with levodopa it can sometimes be reduced by partial replacement with an agonist. It can also be aggravated by concomitant use of anticholinergics.

Diphasic dyskinesia occurs at the beginning or end of dose, or both[27] and is less common than peak dose dyskinesia. It is mainly seen in patients with young age of onset. It is usually much more severe than the peak dose type, often being violently ballistic in character, especially in the legs, and is very difficult to manage. Overlapping doses of levodopa may help in the short term, but often the patient ends up in permanent dyskinetic chaos. Partial replacement by agonists occasionally helps, but some patients prefer to return to taking levodopa three times a day, which gives better predictability, albeit at the expense of more time off.

Off period dystonia—Fixed, often painful, dystonic spasms, usually of one or both feet, may occur on rising in the morning, or when doses are wearing off.[28] These can be averted or helped by taking the first dose of levodopa (perhaps as a dispersible preparation, which works faster) on waking and staying in bed until it works. Other options are night time controlled release levodopa or agonist, an anticholinergic, or an apomorphine injection to turn on rapidly in the morning. If these do not help, baclofen or lithium is sometimes useful.

PSYCHIATRIC SIDE EFFECTS

Virtually the whole spectrum of psychiatric disorder can be encountered in a Parkinson's disease clinic. Psychiatric disturbance often progresses over time from vivid dreams and nightmares, through visual illusions, delusions of presence and visual pseudohallucinations (with retained insight), to true delusions and visual (much less commonly auditory) hallucinations (in which insight is lost). Euphoria, hypomania, hypersexuality, and rarely schizophreniform psychosis can also occur. In addition, about two thirds of patients with fluctuations taking levodopa experience off period dysphoria,[29] comprising panic, anxiety, or depression and even (rarely) psychotic delusions and hallucinations. The symptoms resolve instantaneously when treatment turns the patient on, being replaced by euthymia or sometimes euphoria.

Off period dysphoria is best managed by manipulation of antiparkinsonian drugs. However, sustained depression, which develops at some stage in about a third of patients, may need treatment with an antidepressant.

If a patient develops an organic confusional state or psychosis, antiparkinsonian drugs should be discontinued according to "last in, first out" principle—the last drug added before the problem arose should be stopped first. Otherwise, drugs should usually be stopped in the following order: anticholinergics, selegiline, amantadine, dopamine agonists. The dose of levodopa, which has the best therapeutic index in

relation to psychiatric side effects, should then be progressively tapered. If the patient is still psychotic thioridazine or sulpiride should be given, but these will often cause unacceptable worsening of parkinsonism. In many countries clozapine is then the drug of choice,[30] but in Britain it is licensed for use only in treatment resistant schizophrenia. In the acutely, severely disturbed patient antipsychotic treatment may have to be started immediately, sometimes even using more incisive conventional neuroleptics.

Conclusions

The drug treatment of Parkinson's disease is challenging but highly rewarding. The choice, dose, and timing of several different drugs need to be individually tailored, ideally on the basis of accurate feedback concerning fluctuations, dyskinesia, and other side effects. The broad recommendations presented above are intended as a guide. They should not be followed too rigidly and will probably change in the light of further evidence from clinical trials.

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Lesson of the Week

Cystic fibrosis presenting as hyponatraemic heat exhaustion

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BMJ 1995;310:579-80

Cystic fibrosis is the commonest autosomal recessive disorder in Europe. It can present late with atypical features.[1] Mutations in a gene on chromosome 7 that regulates transmembrane conductance cause the disease.[2] Seventy two per cent of patients with cystic fibrosis are homozygous or heterozygous for eight mutations of the gene.[3] The primary defect is low permeability of cell membranes to chloride ions which affects fluid transport during secretion and absorption by epithelial cells.[4] We report a case of late presentation of cystic fibrosis in a man with the ΔF508 and R117H mutations.

Case report

A 24 year old infantryman was referred after having collapsed twice with hyponatraemia in hot climates. He said that he sweated more than his colleagues in the heat and formed a crust of salt on his skin in hot climates. Before these episodes he had been generally well with no medical history.

In 1991 he was posted to Saudi Arabia, where he underwent heat acclimatisation, which culminated in running 4·8 km after two months. His water intake was greater than his colleagues' during the run. He collapsed immediately afterwards and was admitted to a civilian hospital with nausea, vomiting, dizziness, and muscle cramps. He was posturally hypotensive. Serum electrolyte concentrations were: sodium 116 mmol/l, potassium 2·68 mmol/l, and chloride 57 mmol/l. Liver function tests gave normal results; 1·8 l of urine were collected over 24 hours and urine and plasma osmolalities were 245 mmol/kg. Urinary sodium and potassium excretion was 32·4 mmol/l and 11·8 mmol/l respectively. He was given intravenous normal saline with potassium replacement (3 l over 24 hours), and he made a complete recovery within 48 hours. He returned to a military hospital in the United Kingdom for investigation and underwent extensive biochemical screening, including a formal water deprivation study. The results were normal and diagnosis was deferred.

For the following year he carried out duties that entailed strenuous physical exercise in various temperate countries; he had no adverse effects. In July 1993 he was posted to Cyprus, where temperatures